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FILE 'CAPLUS' ENTERED AT 14:04:00 ON 01 APR 2003
L1 10 S WATSON,?/AU AND GASTRIMMUNE

=> d 1-10 bib,abs

L1 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2002:46090 CAPLUS
DN 137:119898
TI **Gastrimmune**-induced antigastrin-17 antibodies inhibit acid secretion in a rat fistula model
AU Smith, A. M.; Morris, T.; Justin, T.; Michaeli, D.; **Watson, S. A.**
CS The Academic Unit of Cancer Studies, University Hospital, Nottingham, NG7 1AX, UK
SO Alimentary Pharmacology and Therapeutics (2001), 15(12), 1981-1988
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
AB **Gastrimmune** is an immunogenic form of gastrin. It raises in situ antibodies against two proliferative forms of gastrin: amidated and glycine-extended gastrin-17. It has been shown to have a therapeutic action in several in vivo tumor models. Following immunization, due to the complex equil. that exists between the antibodies and gastrin, it is not tech. feasible to assay for free gastrin. To det. the effect of **Gastrimmune**-induced antigastrin antibodies on acid secretion. A rat gastric fistula model was used. Animals (six per group) were immunized with a control immunogen or ascending doses of **Gastrimmune**. Acid output was measured following infusion of increasing doses of gastrin-17 and pentagastrin. **Gastrimmune** -induced antibodies significantly reduced gastrin-17-stimulated acid output compared to control animals (**Gastrimmune** at 200 g/rat vs. control: acid output following 30 ng gastrin-17, 0.01 vs. 0.16, $P < 0.001$; following 120 ng gastrin-17, 0.022 vs. 0.29, $P < 0.001$). **Gastrimmune** significantly inhibits gastrin-17-stimulated acid output. This biol. assay suggests that the antigastrin antibodies effectively bind gastrin-17. In addn. to its use as an antineoplastic agent. **Gastrimmune** may have a role as an acid-decreasing agent in esophagogastric pathol.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2001:287203 CAPLUS
DN 135:330148
TI G17DT - a new weapon in the therapeutic armory for gastrointestinal malignancy
AU **Watson, Sue A.**; Gilliam, Andy D.
CS Academic Unit of Cancer Studies, Division of GI Surgery, QMC, University Hospital, University of Nottingham, Nottingham, NG7 2UH, UK
SO Expert Opinion on Biological Therapy (2001), 1(2), 309-317
CODEN: EOBTA2; ISSN: 1471-2598
PB Ashley Publications Ltd.
DT Journal; General Review
LA English
AB A review with refs. G17DT or **Gastrimmune**, as it was formally known, is an antigastrin 17 immunogen producing neutralizing high affinity antibodies directed against gastrin-17 (G17). Preclin. studies, initiated to identify biol. functionality of G17DT-induced antibodies, confirmed that the antibodies both reduced G17 stimulated gastric acid secretion and inhibited gastrin from interacting with the CCK-2 receptor. Therapeutic

efficacy of both passive and active immunization with G17DT has been established in a no. of tumor systems including both primary and metastatic disease. Furthermore, additive effects with 5-fluorouracil (5-FU)/leucovorin have been confirmed in both colon and gastric tumor models. Phase I/II studies in advanced gastrointestinal (GI) malignancies have shown no systemic or autoimmune reactions to active immunization with G17DT. Use of an optimized dose has yielded a high proportion of responders (> 80%), with minimal side effects and antibody titers measurable within 2-4 wk. Taken together these results suggest that the G17DT immunogen is a promising agent for the treatment of GI cancer and Phase III trials, currently underway, will definitively evaluate this early promise.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2001:125533 CAPLUS
DN 134:293706
TI Hypergastrinemia promotes adenoma progression in the APCMin-/+ mouse model of familial adenomatous polyposis
AU **Watson, Sue A.**; Smith, Andrew M.
CS Academic Unit of Cancer Studies, Department of Surgery, University of Nottingham, Nottingham, NG7 2UH, UK
SO Cancer Research (2001), 61(2), 625-631
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Serum hypergastrinemia promotes the growth of colorectal adenocarcinoma. Some colorectal adenomas express cholecystokinin B/gastrin receptor mRNA, and thus hypergastrinemia may increase progression through the adenoma-carcinoma sequence. This was investigated in the multiple intestinal neoplasia APCMin-/+ mouse. Serum gastrin levels in APCMin-/+ mice were elevated 5-6-fold by oral administration of omeprazole (75 mg/kg). Terminal tumor burden was monitored by onset of anemia. A labeling index was generated by immunohistochem. detection of bromodeoxyuridine incorporation. Serum gastrin was neutralized by antigastrin antibodies raised in situ by use of a gastrin immunogen, **Gastrimmune**. Hypergastrinemia resulted in reduced survival of the APCMin-/+ mice from a median survival of 13 wk in the controls to 10 wk following omeprazole treatment ($P < 0.00001$, log-rank test). The labeling indexes of adenomas from the small and large intestines of omeprazoletreated mice were increased 35 and 29%, resp. ($P < 0.05$ and $P < 0.025$, resp.). **Gastrimmune** immunization reversed both the survival effect and the increased proliferation resulting from serum hypergastrinemia. Hypergastrinemia may promote the progression of existing premalignant colonic lesions by increasing proliferation. Clin. investigations should det. whether this occurs in the human scenario, considering the widespread use of proton pump inhibitors.

RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2001:83356 CAPLUS
DN 135:28767
TI Phase I/II study of G17-DT, an anti-gastrin immunogen, in advanced colorectal cancer
AU Smith, Andrew M.; Justin, Timothy; Michaeli, Dor; **Watson, Susan A.**
CS Academic Unit of Cancer Studies, University of Nottingham, Nottingham, NG7 2UH, UK
SO Clinical Cancer Research (2000), 6(12), 4719-4724
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal

LA English
AB Gastrin is a growth factor for colorectal cancer, and therefore, anti-gastrin hormone therapy has a potential role in treatment of this disease. The gastrin immunogen gastrin-17-diphtheria toxoid (G17-DT; **Gastrimmune**) produces anti-G17 antibodies that were shown to be effective in the treatment of colorectal carcinoma in preclin. models. 50 Patients with advanced colorectal cancer were treated with G17-DT in a multicenter, sequential group, open label Phase I/II study. Primary injections with 2 booster doses were given by i.m. injection. The main aim of the study was to assess the safety and efficacy of the prodn. of antigastrin antibodies. Locally developed and std. WHO toxicity measurements with RIA and Scatchard anal. for antibody assessment were used. 1 Center measured tumor response radiol. 80% Of patients produced a measurable antibody response. Antibodies of high affinity (median Kd, 0.295 nm; interquartile range, 0.16-0.41 nm) were detected between 4 and 12 wk after primary injection. The antigen binding capacity was high at 2.8 .times. 10-9 M (interquartile range, 5.1 .times. 10-10 to 7.25 .times. 10-9 M). The treatment was well tolerated with no systemic side effects seen. Myalgia at the injection site was seen in 46% of patients with severe pain caused by the formation of a sterile abscess seen in 14% of patients. The abscesses were all drained under ultrasound guidance, and the patients recovered fully within 6 wk. No radiol. responses were seen, but 2 patients had stable disease. G17-DT immunization produces anti-G17 antibodies in patients with advanced colorectal cancer. The antibodies were of an affinity high enough to compete with the cholecystokinin B/gastrin receptor for G17 binding with adequate capacity to neutralize postprandial gastrin surges. Addnl. dose-ranging studies were performed in patients with gastric cancer using 100- and 200-.mu.g doses of G17-DT formulated without adjuvant and the emulsifier Al monostearate. In addn., the effect of immunizing at different time intervals was detd.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 2000:18901 CAPLUS
DN 132:277885
TI A comparison of the therapeutic effectiveness of gastrin neutralisation in two human gastric cancer models: relation to endocrine and autocrine/paracrine gastrin mediated growth
AU **Watson, S. A.**; Morris, T. M.; Varro, A.; Michaeli, D.; Smith, A. M.
CS Academic Unit of Cancer Studies, Department of Surgery, University of Nottingham, Nottingham, UK
SO Gut (1999), 45(6), 812-817
CODEN: GUTTAK; ISSN: 0017-5749
PB BMJ Publishing Group
DT Journal
LA English
AB Gastrin is a growth factor for established tumors. To investigate the therapeutic effect of antibodies, raised against the **Gastrimmune** immunogen, which neutralize the glycine extended and carboxy amidated forms of gastrin 17 in two human gastric cancer models, MGLVA1 cells (which have a gastrin autocrine/paracrine phenotype) and ST16 cells (which have an endocrine phenotype) were injected into the peritoneal cavity of SCID mice. Peritoneal tumors, ascites, and cachexia formation occurred, with the monitored endpoint being morbidity. In MGLVA1 cells, i.v. administration of antibodies raised against **Gastrimmune** increased the 50% median survived by 25% at three different initial cell seeding concns. (1 .times. 106-5 .times. 105 per mouse). In ST16 cells, the effect of **Gastrimmune**-induced antibodies on time to morbidity was greatest at the lowest cell seeding concn. (5 .times. 105 cells/mouse) with the 50% median survival increased by 74% and overall survival achieved in 38% of the mice. Thus, **Gastrimmune** may have potential therapeutic benefit on gastrin-sensitive gastric tumors and

may interact with both endocrine and autocrine mediated growth pathways.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1999:591097 CAPLUS
DN 132:106683
TI Antibodies raised by **gastrimmune** inhibit the spontaneous metastasis of a human colorectal tumour, AP5LV
AU **Watson, S. A.**; Michaeli, D.; Morris, T. M.; Clarke, P.; Varro, A.; Griffin, N.; Smith, A.; Justin, T.; Hardcastle, J. D.
CS Cancer Studies Unit, Department of Surgery, University Hospital, Nottingham, NG7 2UH, UK
SO European Journal of Cancer (1999), 35(8), 1286-1291
CODEN: EJCAEL; ISSN: 0959-8049
PB Elsevier Science Ltd.
DT Journal
LA English
AB Both precursor forms of gastrin and mature amidated gastrin peptides can enhance proliferation of colorectal tumors and may regulate growth in an autocrine manner. The purpose of this study was to evaluate the effect of neutralization of precursor and amidated gastrin on primary and secondary in vivo growth of a human colorectal tumor. The human colorectal cell line, AP5LV, when injected into the muscle layer of the abdominal wall of severe combined immunodeficient (SCID) mice, grows as a well-vascularised primary tumor and metastasizes to the lung. AP5LV expressed the precursor gastrin forms; progastrin and glycine-extended gastrin and gastrin/CCKB receptors, as assessed by immunocytochem. **Gastrimmune** is a gastrin immunogen in which the amino terminus of the gastrin-17 mol. is linked to diphtheria toxoid and induces antibodies which neutralise the amidated and glycine-extended forms of gastrin-17. Rabbit antiserum, raised against **Gastrimmune**, was administered i.v. into SCID mice bearing AP5LV tumors. Control animals were treated with antiserum raised against diphtheria toxoid only. Antibodies raised against **Gastrimmune** significantly limited the growth of primary AP5LV tumors, as assessed by median cross-sectional area (controls = 244 mm2; antibody-treated = 179 mm2; P = 0.033). In addn., **Gastrimmune** -induced anti-serum limited the growth of lung metastasis as assessed by nodule no. (controls = 3.5; antibody-treated = 1.0; P = 0.0001) and nodule cross-sectional as assessed by image anal. (controls = 11.9 mm2; antibody-treated = 3.75 mm2; P = 0.0064). In conclusion, in vivo neutralization of gastrin forms, which may potentially be fueling growth by an autocrine pathway, inhibited both primary growth and, to a greater degree, lung metastasis of a human colorectal tumor cell line. Immunization against tumor-assocd. gastrin forms may provide an effective therapy for advanced colorectal cancer.
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1999:240647 CAPLUS
DN 131:67740
TI A comparison of an anti-gastrin antibody and cytotoxic drugs in the therapy of human gastric ascites in SCID mice
AU **Watson, Sue A.**; Michaeli, Dov; Grimes, Stephen; Morris, Teresa M.; Varro, Andrea; Clarke, Philip A.; Smith, Andrew M.; Justin, Tim A.; Hardcastle, Jack D.
CS Cancer Studies Unit, Department of Surgery, University of Nottingham, Nottingham, NG7 2UH, UK
SO International Journal of Cancer (1999), 81(2), 248-254
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English

AB The therapeutic effect of antibodies raised by the immunogen **Gastrimmune** was compared with both a CCKB/gastrin receptor antagonist, CI-988, and 5-fluorouracil/leucovorin in a gastric cancer model. The human gastric ascites cell line, MGLVA1asc, produced and secreted progastrin and glycine-extended gastrin as detd. by RIA and immunocytochem. Cells were also stained with an antiserum directed against the human CCKB/gastrin receptor. MGLVA1asc cells were injected i.p. into SCID mice. Antibodies raised by **Gastrimmune** immunization of rabbits (affinity for G17 of 0.15 nM and GlyG17 of 0.47 nM) were passively infused i.p. and significantly enhanced survival by up to 5 days ($p = 0.0024$ from vehicle controls). The enhancement in survival was not significantly different from that achieved by treatment with 5-fluorouracil and leucovorin. A CCKB/gastrin receptor antagonist, Cl-988, did not affect survival with cells injected at 7.5.times.105 cells/mouse but significantly increased the survival of mice injected with a lower cell inoculum of 5.times.105 cells/mouse from 30 to 35 days ($p = 0.0186$). At this lower inoculum antibodies raised by **Gastrimmune** induced complete survival in 2 animals with the remaining dead by day 36 ($p = 0.0022$). Thus, both endocrine and autocrine pathways mediated by precursor and mature gastrin mols. may be jointly operational in the gastric cancer scenario and may be important targets for therapeutic agents.

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1998:155847 CAPLUS
DN 128:278696
TI Pre-clinical evaluation of the **Gastrimmune** immunogen alone and in combination with 5-fluorouracil/leucovorin in a rat colorectal cancer model
AU **Watson, Susan A.**; Michael, Dov; Justin, Timothy A.; Grimes, Stephen; Morris, Teresa M.; Robinson, Graham; Clarke, Philip A.; Hardcastle, Jack D.
CS Cancer Studies Unit, Department of Surgery, University Hospital, University of Nottingham, Nottingham, UK
SO International Journal of Cancer (1998), 75(6), 873-877
CODEN: IJCNAW; ISSN: 0020-7136
PB Wiley-Liss, Inc.
DT Journal
LA English
AB Mature and post-translational precursor gastrin forms are growth factors for colorectal tumors. The immunogen **Gastrimmune** is composed of the amino terminus of gastrin-17 linked to diphtheria toxoid and raises antibodies in situ which neutralize amidated and glycine-extended gastrin-17. The aim of the study was to det. the effect of treatment with 5-fluorouracil(5-FU)/leucovorin on the antibody titers induced by **Gastrimmune** and the effect of combination therapy on the growth of the rat colon tumor DHDK12. **Gastrimmune** was administered to rats s.c. at 3 weekly intervals. The rat colon tumor line DHDK12 was injected into the abdominal wall of BDIX rats. Combinations of 5-FU/leucovorin were injected i.v. on days 1, 3 and 5, with the cycle repeated every 4 wk. Antibody titers were measured by an ELISA technique. Antibody titers were followed for 40 wk after **Gastrimmune** (500 .mu.g .cntdot.mL-1) immunization, with titers peaking between 10 and 20 wk after a single immunization and falling by week 30. At termination, no effect was obsd. on either the histol. appearance of the gastro-intestinal tract or the proliferation of the colonic mucosa. Pre- and post-treatment with 5-FU/leucovorin (30 mg.cntdot.kg-1) had no effect on the kinetics and level of antibody response to **Gastrimmune**. **Gastrimmune** (200 .mu.g.cntdot.ml-1) and 5-FU/leucovorin combinations (12.5 and 20 mg.cntdot.kg-1) increased the therapeutic effects on the in vivo growth of DHDK12 tumors when compared to the agents given singly. **Gastrimmune** immunization may be a therapeutic option for the

treatment of colorectal cancer in combination with 5-FU/leucovorin.

L1 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1996:104643 CAPLUS
DN 124:221116
TI **Gastrimmune** raises antibodies that neutralize amidated and glycine-extended gastrin-17 and inhibit the growth of colon cancer
AU **Watson, Susan A.**; Michaeli, Dov; Grimes, Stephen; Morris, Teresa M.; Robinson, Graham; Varro, Andrea; Justin, Timothy A.; Hardcastle, Jack D.
CS Cancer Studies Unit, University of Nottingham, Nottingham, NG7 2UH, UK
SO Cancer Research (1996), 56(4), 880-5
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The effect of gastrin neutralization was evaluated on the in vivo growth of the rat colon line, DHDK12, which expressed cholecystokinin B/gastrin receptors and secreted glycine-extended gastrin-17 (G17). Gastrin neutralization was achieved by administration of the immunogen, **Gastrimmune**, which is composed of the amino terminal portion of G17 linked to a diphtheria toxoid. A rat-specific version of **Gastrimmune** was used to preimmunize rats, with control animals receiving diphtheria toxoid only. The antibodies raised neutralized both carboxy-amidated and glycine-extended G17. The tumor was implanted into the muscle layer of the abdominal wall, and rats immunized with **Gastrimmune** had significantly reduced median cross-sectional tumor areas (70.2% redn.) and wts. (56.5% redn.) when compared to control rats. Histol. anal. revealed that the tumors had an enhanced degree of necrosis with the area of viable tumor in the **Gastrimmune**-immunized rat reduced to 40.3% compared to 58.6% in the control rats. Immunization with **Gastrimmune** raised antibodies that inhibited the growth of a rat colon tumor. This could have been mediated by neutralization of both serum G17 and cell-assocd. precursor gastrin mols.

L1 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1995:544562 CAPLUS
DN 122:312587
TI Anti-gastrin antibodies raised by **gastrimmune** inhibit growth of the human colorectal tumor AP5
AU **Watson, Susan A.**; Michaeli, Dov; Grimes, Steven; Morris, Teresa M.; Crosbee, David; Wilkinson, Mark; Robinson, Graham; Robertson, John F.R.; Steele, Robert J.C.; Hardcastle, Jack D.
CS Department Surgery, Queen's Medical Centre, Nottingham, UK
SO International Journal of Cancer (1995), 61(2), 233-40
CODEN: IJCNAW; ISSN: 0020-7136
DT Journal
LA English
AB The neutralizing ability of rabbit anti-gastrin-17 (G17) antiserum raised by **Gastrimmune**, an immunogen constructed of the N-terminal portion of human G17 conjugated to diphtheria toxoid (DT), was evaluated. The anti-serum (denoted anti-G17: DT) was shown to displace 125[I] G17 from the gastrin receptors on AR42J cells. The therapeutic effect of the rabbit anti-G17:DT anti-serum was evaluated on a freshly derived human colorectal cancer cell line, AP5, which was shown to express both gastrin receptors and gastrin immunoreactivity as assessed by immunocytochem. Rabbit anti-G17:DT anti-serum was shown to block basal in vitro growth of AP5 cells when used at an antigen binding capacity of 3.75 .times. 10-9 M. The same diln. of anti-serum completely reversed growth stimulated by human G17 at concns. of 1 .times. 10-10 and 1 .times. 10-9 M but did not inhibit growth at 1 .times. 10-8 M G17. When AP5 was grown as a xenograft in nude mice, the sensitivity to the proliferative effect of human G17 was maintained. In addn., the basal growth of AP5 xenografts was significantly reduced by i.v. infusion of rabbit anti-G17:DT anti-serum

when compared to treatment with rabbit anti:DT control anti-serum. Thus, anti-G17:DT antibodies raised by **Gastrimmune** may be of clin. value in gastrin-sensitive tumors.